Review

Psoriatic arthritis: one year in review 2022

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ABSTRACT

Psoriatic arthritis is a systemic autoimmune disease, in which a characteristic heterogeneous inflammatory involvement of entheses and both peripheral and axial joints tends to be associated with different clinical features, in particular skin or nail psoriasis, but also inflammatory bowel diseases, or acute anterior uveitis. Patients with PsA are at higher risk of developing comorbidities, in particular metabolic syndrome, with a significant impact on their quality of life. Although the advanced knowledge in the pathogenetic mechanisms of PsA helped in developing an abundant therapeutical armamentarium, the available drugs might still show a suboptimal efficacy. However, the frontier of "personalised medicine" could promote further future improvement in the quality of care of patients. In this paper we reviewed the literature on PsA of 2020 and 2021 (Medline search of articles published from 1st January 2020 to 31th December 2021).

Introduction

Together with ankylosing spondylitis (AS), one of the main members of spondyloarthritides (SpA) is Psoriatic Arthritis (PsA), a systemic autoimmune disease, in which a characteristic heterogeneous inflammatory involvement of entheses and both peripheral and axial joints tends to be associated with skin or nail psoriasis (PsO), inflammatory bowel diseases (IBD), and acute anterior uveitis (AAU).

It is well known that patients with PsA are at a higher risk of developing some comorbidities, in particular, metabolic syndrome, mood disorders, osteoporosis, malignancies and fibromyalgia.

Taking into account the great complexity of this clinical condition, the concept of "Psoriatic Disease" (PsD) was stated to better describe the multifaceted clinical pictures that PsA patients might show (1-3).

Due to the impact that PsD could have in everyday life, the disease may also cause work disability and a significant impairment of patients' quality of life (QoL) (4).

Although advanced knowledge in the pathogenetic mechanisms of PsD (both genetic susceptibility, environmental factors and altered inflammatory responses) has helped to develop a considerable therapeutical armamentarium, the currently available drugs still show suboptimal efficacy. However, the frontier of "personalised medicine" could promote future improvement in the quality of care (QoC) of patients (5, 6).

In this paper we review the literature on PsA of the last two years; finally, a brief section will be dedicated to the impact of COVID 19 on disease burden.

Methods

Following our regular annual reviews on different aspects of rheumatology (7-11) we will here provide a critical digest of the recent literature on PsA of 2020 and 2021 (Medline search of articles published from 1st January 2020 to 31th December 2021). In particular, we performed an on-line search on MESH database, using as key terms "blood", "complications", "diagnostic imaging", "drug therapy", "economics", "epidemiology", "etiology", "genetics", "mortality", "prevention and control", "psychology", "therapy".

Pathogenesis

The knowledge of the pathogenetic mechanisms at the basis of PsA onset and of the relation between joint disease and the involvement of other domains is still uncomplete.

The role of T cell dysregulation in PsA has been particularly investigated in two recent studies. The first one by Gertel *et al*. showed that PsA activity

was associated with impaired levels of lymphocyte-activation gene (LAG)-3 receptor expression on $CD4^+$ lymphocytes. The authors also noted TNF inhibitors (TNFi) could up-regulate CD4-LAG-3+ levels, with possible improvement on the control of disease activity (12). Considering that phosphodiesterase 4 (PDE4) could be involved in the cleavage of the soluble form of CD40L (sCD40L), a second study by Venerito *et al*. investigated the effect of Apremilast (APR), a PDE4 inhibitor, on sCD40L levels and PsA activity. Interestingly, they found that PsA low disease activity/remission and sCD40L were independently associated (13).

A metabolome analysis on patients with PsA, cutaneous PsO and healthy controls showed a significant difference in plasma levels of tyramine and mucic acid in these disorders thus shedding new light on possible specific biomarkers that are potentially helpful in clarifying distinct pathogenetic pathways in PsA and PsO (14).

Finally, an international collaborative study on patients with AS and axial PsA showed that HLA-B27 positivity was a risk factor for radiographic damage accrual; in particular, it seemed to be associated with the development of symmetric and marginal syndesmophytes, but not with a symmetric sacroiliitis (15). An Austrian study on PsA patients from the Infliximab Multinational Psoriatic Arthritis Controlled Trial confirmed disease activity, on both clinical and biochemical parameters, which favoured structural progression (16).

Take home messages

- T cells dysregulation could have a role in PsA severity (13, 14);
- Metabolome analysis could clarify some of PsA pathogenetic mechanisms (15);
- Damage accrual in PsA patients seems to be related not only with disease activity, but also with HLA-B27 positivity (16, 17).

Imaging

Imaging techniques are crucial in characterising and monitoring the wide range of articular and periarticular features of PsA patients.

Dactylitis is one of the most typical lesions of PsA, and is characterised by different kinds of articular and periarticular involvement, in particular arthritis, tenosynovitis, subcutaneous soft tissue oedema and peritendon extensor inflammation. In 2020 a DACTylitis glObal Sonographic (DACTOS) score was developed to globally assess thesonographic elementary lesions of hand dactylitis. The DACTOS score showed a good reliability and a potential usefulness both for research and clinical purposes, due to its sensitivity to change, and its correlations with PsAclinical parameters (17, 18).

In the ACHILLES trial, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) PsA magnetic resonance imaging (MRI) scoring system (PsAMRIS), developed for evaluating inflammation and damage at hands' entheseal sites, was adapted to score heel enthesitis, assessing bone oedema length and locating bone erosions. The adapted score showed good specificity, reliability and sensitivity to change (19).

The enthesopathy of the distal interphalangeal (DIP) joint was recently studied by using high-resolution peripheral quantitative CT and ultrasound. The Authors found that psoriatic onycholysis was associated with development of bone erosions and extensor tendinopathy signs at DIP levels, thus highlighting a possible link between onycholysis and PsA severity (20).

An Italian research study group, confirmed clinical and clinimetric assessments tend to overestimate the prevalence of active enthesitis in fibromyalgia, while ultrasound evaluation could be useful to distinguish between pain at entheseal sites due to fibromyalgia or related to enthesitis (21).

A prospective observational cohort study by Feld *et al*. showed that more than 40% PsA patients had at least unilateral grade 2 SI (Uni2SI) and that more than 30% had a modified New York Ankylosing Spondylitis (mNY AS) SI. Risk factors for the progression from Uni2SI to mNY AS SI were a younger age at disease onset, a less degenerative disc disease, a worse peripherical radiographic damage, a worse PsO, a higher erythrocyte sedimentation rate and a shorter disease duration. These data showed that radiographic mNY AS criteria might be suitable to characterise SI in PsA (22).

Take home messages

- The DACTOS score showed its validity in dactylitis evaluation both in research and clinical practice settings, while an adapted PsAMRIS seemed to be a useful tool to evaluate Achilles tendon enthesitis (17-19);
- Psoriatic onycholysis could be a sign of more severe forms of PsA (20);
- Ultrasound study helps rheumatologists to distinguish between pain at entheseal sites due to fibromyalgia or related to enthesitis (21);
- Radiographic mNY AS criteria are suitable to evaluate SI in PsA patients (22).

Clinical picture

Some evidence emerged from the literature about clinical features of patients with PsA.

Interestingly, Israelian PsA patients showed a prevalence of non-radiographic and radiographic SI of respectively 11% and almost 30%; in particular in the first case, inflammatory back pain was confirmed as a not sensible indicator (23).

Swedish patients with PsA, on the other hand, had lower incidence rate ratios for the development of AAU and IBD than both patients with AS or Undifferentiated SpA; moreover, AAU did not correlate with gender (24).

Interestingly, data from a multicentre observational study on PsA patients showed that active enthesitis could increase the risk of dactylitis and chronic back pain and was associated with worse QoL parameters (25).

A Turkish research group found that more than 40% of PsA patients had carpal tunnel syndrome, with a significantly higher frequency than healthy controls (26).

As regards CV features, a recent study on patients with chronic arthritis showed that in patients with PsA, arterial stiffness (evaluated through both aortic stiffness index and carotid dis-

tensibility) was strictly associated with left diastolic function and left ventricular mass (27).

Take home messages
- Inflammatory back pain does not seem to be a good indicator of non radiographic SI in PsA patients (22);
- PsA patients have a lower risk of IBD and AAU (23);
- Active enthesitis increased the risk of dactylitis, chronic back pain and worse QoL (25);
- PsA patients seem to be at higher risk of developing carpal tunnel syndrome (26);
- Arterial stiffness is associated with left ventricular mass and function in patients with PsA (27).

Comorbidities

Our recent review of the literature underlined the central role of CV risk factors in patients with PsA.

In a longitudinal observational study on overweight PsA patients, the high prevalence of comorbidities such as hypercholesterolaemia, arterial hypertension, hyperuricaemia and type 2 diabetes mellitus was confirmed (28).

Interestingly, a recent cross-sectional observational study on subjects affected by PsA and/or PsO showed a significantly higher prevalence of hyperlipidaemia (HL) among PsA patients compared with only PsO; therapy with conventional synthetic (cs)- or biologic (b)-DMARDs seemed to protect from HL, thus suggesting that a better control of systemic inflammation could reduce its adverse impact on the CV system (29).

Data from a cross-sectional, observational and comparative study on PsA patients showed that those with nail PsO had higher carotid intimal media thickness values and confirmed that nail involvement could be an independent risk factor for carotid plaque formation (30).

Factors linked to inflammation such as clinical enthesitis and erosive burden of PsA could be associated with subclinical atherosclerosis (SA) development. A Spanish observational study showed that 25% of patients had signs of SA, significantly less frequently encountered in those achieving a minimal disease activity (MDA) status (31). On the other hand, Ballegaard *at al*. reported that obesity, hypertension, widespread pain and a Charlson Comorbidity Index ≥1 seemed to compromise the control of disease activity (32).

Finally, a Danish matched-cohort study highlighted the risk of a serious infective adverse event (AE) in patients with chronic arthritis beginning bDMARDs was four times that of the general population. Moreover, the authors produced a prediction model for serious infection including age, previous serious infection within the last 5 years, pulmonary disease, diabetes, IBD, myocardial infarction and glucocorticoid use (33).

Take home messages
- Comorbidities associated with a higher CV risk are confirmed as prevalent in PsA patients (28, 29);
- Nail psoriatic involvement seems to be an independent risk factor for atherosclerosis in PsA (30);
- A worse control of PsA activity is associated with a higher CV risk (31, 32);
- PsA patients who should start b-DMARDs have a higher risk of serious infections (33).

Clinimetrics

Data from a recent trial on PsA patients treated with methotrexate (MTX) in monotherapy, or etanercept (ETN) in monotherapy, or with a combination therapy of MTX plus ETN, confirmed that a composite clinimetric measure could be more sensitive in quantifying changes in disease activity and damage and patients' QoL (34).

Data from PsA patients enrolled in the FUTURE 2 trial showed that those achieving Disease Activity in Psoriatic arthritis (DAPSA) remission (REM) or Low Disease Activity (LDA) and those in MDA had better improvements in PROs than those with a more active PsA, thus confirming not only the usefulness of these clinimetric indices in evaluating disease activity and response to therapy, but also their accordance with health-related outcomes (35).

Data from two randomised clinical trials were evaluated to establish the psychometric properties of the fatigue numeric rating scale (NRS). The authors demonstrated its validity and responsiveness in PsA patients, thus supporting its use in clinical trials and routine clinical practice. As expected, fatigue improved after a reduction in disease activity; interestingly, a 3-point improvement in fatigue NRS was demonstrated, representing a clinically significant change in PsA assessment. However, validation in patients with low levels of disease activity is still needed (36).

Take home messages
- Composite clinimetric indices are useful to evaluate both disease activity and damage and tend to correlate with health-related outcomes (34, 35);
- NRS may provide a good evaluation of PsA patients' fatigue (36).

Quality of life

The association between PsA and fatigue is well known. An Asian study not only confirmed a higher prevalence of fatigue among patients with PsA, but also showed a significant correlation with both DAPSA and Psoriasis Area and Severity Index (PASI) scores, thus suggesting that an optimised control of disease activity could improve fatigue in these patients (37).

Similarly, a cross-sectional survey on PsA patients of the DANBIO registry confirmed that disease activity seemed to significantly impact on fatigue, together with disease duration and chronic pain, more related to central pain sensitisation or to joint damage, than to inflammation (38).

Involvement of sleep quality may often be observed in PsA. Data from a Spanish multicentre study investigating sleep disorders in patients with Ax-SpA and PsA showed that mood disorders (in particular depression), poor QoL and active disease seemed to be risk factors for the development of insomnia (39). On the contrary, data from a multicentre observational study, underlined that pain and anxiety were the major determinants of sleep impairment in PsA, independently of disease activity (40).

Bavière and collegues showed that the type of comorbidity seemed to influence PsA patients' QoL more than the number of comorbidities; in particular, anxiety seemed to compromise mental health (41).

Take home messages

- Disease activity, disease duration and chronic pain seem to significantly impact on the occurrence of fatigue in PsA patients (37, 38);
- Sleep impairment in PsA could be associated with mood disorder; whether disease activity has a significant role in its development is still unclear (39, 40).

Therapy

MTX and TNFi

A monocentric study confirmed that MTX gastrointestinal side effects could be significantly alleviated by switching from folic to folinic acid supplementation, with a concomitant improved persistence on therapy (42).

An American retrospective cohort study on PsA patients showed that the first-line treatment was monotherapy in over 90% of patients, with a great prevalence of MTX use. Although csDMARDs were the less expensive drugs, they had the highest interruption rates and the lowest persistence on therapy. As expected, the most frequent second-line therapy was MTX plus TNFi combination (43).

Another retrospective cohort study aimed to explore how to taper TNFi in both PsA and axSpA patients with a stable disease control. The authors found TNFi tapering was associated with a higher rate of flares in PsA patients (44).

A small real-life study evaluating efficacy, safety and PROs outcomes of Certolizumab Pegol (CTZ) in a cohort of PsO and PsA patients, confirmed the efficacy of the drug in both the subgroups, with a good safety profile; the authors observed a significant improvement in PROs outcomes, particularly for cutaneous domains (45).

A *post-hoc* analysis of a phase 3 RCT comparing MTX and ETN monotherapies or combination therapy, showed a significantly lower PRO improvement in the MTX-monotherapy group (46).

A Spanish, real-life study, observed that Benepali, one of the ETN biosimilar drugs, could have a better efficacy profile and retention rate than the originator in PsA and SA patients, with a comparable adverse AE rate (47).

The results of two phase-3 studies showed that Adalimumab (ADA) originator and one of its biosimilars Hyrimoz showed comparable improvement in PRO outcomes in patients with PsO, PsA and rheumatoid arthritis (RA); no worsening was observed after switching between biosimilar and originator (48).

An Italian real-life analysis on ABP-501, another ADA biosimilar, in treating PSO and PsA patients, showed a significant cutaneous improvement if patients were originator-naive (49).

Two Japanese studies confirmed the efficacy of ADA in treating axial involvement and in improving disease control on both articular and cutaneous domains in patients with a previous inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs) (50, 51).

A recent retrospective, observational study investigated the effectiveness and safety of Infliximab (IFX), Ustekinumab (UST) and Golimumab (GOL) in PsA patients showing similar efficacy and AEs rates. IFX had the higher retention rate and its withdrawal was primarily due to AEs, while UST and GOL were stopped mostly because of a loss of response (52).

On the contrary, the GO-VIBRANT trial, demonstrated GOL efficacy in patients with active PsA, with response outcomes maintained also in those patients initially treated with placebo (53). Moreover, in the GO-PRACTICE study, it was observed that GOL efficacy and persistence on therapy were better in bDMARD-naive patients (54).

A Portuguese study showed the efficacy of MTX/GOL combination therapy to treat dactylitis, according to both the Dactylitis Severity Score and the Leeds Dactylitis Index response (55).

A lower DAPSA, younger age, higher PCR values and a longstanding disease seemed to be clinical factors favouring the achievement of MDA in PsA patients treated with GOL (56).

Possibly due to a direct GOL effect in reducing osteoclast activity, the treatment of PsA patients with IV-GOL showed a significant improvement in the erosive burden of the disease, with a reduction of radiographic progression, even in those patients who did not achieve LDA status (57).

An American surveillance study on GOL in patients with chronic arthritis did not report any new safety concerns (58), while data from the GO-PRACTICE trial highlighted among RA, SA and PsA patients, that the latter had the lowest AE rates, but the highest rate of severe AEs (54).

Small molecules

Tofacitinib (TOFA) was effective in reducing pain in PsA patients, both in unidimensional and in multidimensional evaluation scales, with a duration of benefit of at least 6 months (59).

A multicentric study recently confirmed its efficacy also in patients who did not respond to csDMARDs plus Apremilast (APR) or bDMARDs, with a steroid-sparing effect, a satisfactory retention rate and a good safety profile; however, there was no significant PASI improvement (60).

The global efficacy of the drug and its dyslipidaemic effect appeared independent of patients BMI; however, SF-36 domains and FACIT global values seemed to be negatively influenced by a BMI ≥35 kg/m^2, perhaps due to the high lipophilicity of the drug (61).

The SELECT-PsA1 study showed that the efficacy of Upadacitinib (UPA) in musculoskeletal and cutaneous domains was maintained up to the 56th week. Both UPA 15 and UPA 30 mg groups showed a better control in disease activity than the ADA control group, and the patients who switched from placebo to UPA showed similar disease improvements to patients firstly randomised to UPA. The total number of AEs and severe infective AEs were higher in the UPA 30 mg group (62, 63).

UPA pharmacokinetic was similar in PsA and RA patients, regardless of the concomitant use of csDMARDs (63).

APR 30 mg x 2/day was significantly more effective in PsA patients with lower levels of disease activity. Mease and colleagues also noted that clinical

DAPSA improvements were associated with better PROs outcomes (64).
The efficacy of the drug was confirmed in both musculoskeletal and psychological domains also in Belgian patients; the AEs observed were mainly mild headache or diarrhoea, as already shown in previous studies (65).
An Italian study showed that PDE4 inhibition had better outcomes in those patients with diabetes mellitus and low LDL levels; moreover, they observed a reduction in glycaemia and cholesterol levels after starting therapy, in agreement with previous data from the literature (66). On the contrary, a history of malignancies and a previous therapy with bDMARDs could reduce cutaneous response (67).
Finally, an American study on PsA bDMARDs-naive patients demonstrated that those who initiated APR therapy had comparable switch rates, days to switch and overall adherence than those who initiated a bDMARD; however, APR was associated with significantly lower healthcare costs than biologics (68).

IL17-inhibitors

The SPIRIT head-to-head trial demonstrated that Ixekizumab (IXE) seemed to be superior to ADA for simultaneous achievement of ACR50 and PASI100, with faster effects seen until week 24; moreover, its efficacy appeared consistent for 52 weeks either as monotherapy or in combination with csDMARDs (69, 70).
The SPIRIT-P1 and -P2 trials confirmed it was effective respectively in PsA patients who were biologic-naive and in those with an inadequate response to one or two TNFi (71, 72). In addition, in a *post-hoc* analysis, Combe *et al*. confirmed sustained efficacy both in monotherapy and in combination with MTX, with a good safety profile (73).
Data from Manfreda *et al*. reinforced these results also in a real-life clinical setting, both on skin lesions and on articular symptoms of PsA. Moreover, a high proportion of patients who achieved a skin clearance at six months tended to maintain the improvement over time. Accordingly, LDA status was rapidly reached within the first 6 month of treatment and maintained during the follow-up period (74). Orbai *et al*. demonstrated early and sustained improvement also in PRO outcomes (75).
Taking into account the safety profile of IXE, Combe *et al*. confirmed that a suitable long-term treatment for PsA could be considered; indeed, they found the most common infections were upper respiratory tract infections, nasopharyngitis and bronchitis, while opportunistic infections were limited to oral and oesophageal candida and localised herpes zoster. No suicide or self-injury-related behaviours were reported. Moreover, the incidence of major adverse CV events and malignancy did not increase with longer IXE exposure (76).
MAXIMISE was the first randomised controlled trial which demonstrated the efficacy of Secukinumab (SEC) 300 mg and 150 mg in the management of the axial manifestations of PsA (77).
The FUTURE 5 trial showed sustained clinical efficacy and consistent safety of both SEC 300 and 150 mg, with or without loading dose, in patients with active PsA; a potential benefit from dose escalation in patients whose symptoms were not adequately controlled with SEC 150 mg was observed (78). Moreover, data from this trial demonstrated that up to 92% of patients did not show any radiographic damage accrual (79).
Based on the results of the FUTURE trial, Pournara *et al*. used Machine Learning, a form of artificial intelligence, and identified seven PsA clusters of patients, aimed at tailoring the treatment choice on the basis of disease characteristics (80).
The EXCEED study, a head-to-head trial evaluating the efficacy and safety of SEC *versus* ADA as first-line biological monotherapy showed that SEC did not meet statistical significance for superiority *versus* ADA in the primary endpoint of ACR20 response at week 52. However, SEC was associated with a higher treatment retention rate than ADA (81). On the contrary, Lindstrom *et al*. did not observe any significant differences in treatment retention rate or response between SEC and ADA, regardless of the line of treatment (82). As expected, higher persistence rates were found in patients taking SEC as first-line therapy (83).
Also SEC efficacy and safety were confirmed in a real-life setting, both in PsA and SA. In particular, SEC was effective in reducing the severity and frequency of enthesitis and in minimising the concomitant use of csDMARDs and glucocorticoids. Interestingly, the authors observed a lower response in PsA patients with metabolic syndrome (84). Similar results from routine clinical practice came from a Japanese study conducted by Fujita *et al*. (85).
Kampylafka *et al*. demonstrated that responses in pain and physical activity-related PROs to SEC were more pronounced in established PsA than in patients with very early disease; on the contrary, effects on PROs related to general health perception, emotional and mental well-being improved independently of disease duration (86).
Finally, Deodhar *et al*. demonstrated a very low incidence of immunogenicity of SEC in patients with PsA and AS by dosing the treatment-emergent antidrug antibodies, with no association with any AE or loss of drug efficacy (87).
Brodalumab is an inhibitor of interleukin-17 receptor subunit A. The AMVISION-1 and AMVISION-2 phase III trials showed its efficacy and safety in patients with active PsA and inadequate response or intolerance to conventional treatment. It showed rapid and significant improvements in articular, entheseal and cutaneous domains and in health-related parameters *versus* placebo, with a good safety profile (88).
Bimekizumab, a monoclonal antibody that neutralises IL-17A and IL-17F, can be considered a potential novel therapeutic approach in PsA. BE ACTIVE, a randomised, double-blinded, placebo-controlled phase 2b study, showed significant improvements in ACR50 with an acceptable safety profile in patients with active disease (89).

IL12-23 inhibitors

The IL-12/23 axis can be inhibited with Ustekinumab (UST) that blocks the p40 subunit shared by the two cytokines.
The PSUMMIT 1 and 2 trials demonstrated the efficacy of UST for articular and cutaneous involvement, in patients

with active PsA. Helliwell *et al*. confirmed its efficacy also in the treatment of spondylitis, *versus* placebo, in TNFi-naive patients, particularly in those HLA-B27 positive (90).

PsABio (NCT02627768), an international, prospective, observational, cohort study providing real-world observational data on outcomes of patients starting treatment with either UST or TNFi, showed that they both improved disease activity measures. In particular, higher BMI, higher cDAPSA and chronic widespread pain seemed to negatively influence TNFi efficacy, while female sex, CV comorbidities and enthesitis seemed to compromise the response to UST (91).

Starting from the evidence showing that UST could have modest efficacy in treating PsA joint disease, Nerviani *et al*. analysed the gene expression of the IL-23 axis in skin and synovial tissue from active PsA patients, and observed that IL-23A/R and IL-12-B were expressed at a high level in lesional skin, but heterogeneously in the synovium. These data could suggest that synovial molecular pathology might be useful to identify patients with a greater chance of responding to IL-23 inhibitors (92).

The KEEPsAKE trial demonstrated that Risankizumab, an IL-23 inhibitor, could significantly improve signs and symptoms of PsA, for both joints, skin and nail manifestations, with a relatively good safety profile. Risankizumab could therefore represent an additional therapeutic option for patients who are non-responders to standard therapies (93).

Tildrakizumab is a high-affinity anti-IL23p19 monoclonal antibody approved for plaque psoriasis treatment. Maase *et al*. demonstrated its efficacy in treating arthritis and PsO, with no significant improvements in dactylitis and enthesitis. Tildrakizumab was generally well tolerated, with no report of systemic fungal infections, IBD occurrence, or major adverse cardiac events (94).

Guselkumab (GUS), an IL-23 p19 subunit inhibitor, demonstrated sustained improvements in signs and symptoms of active PsA (95). These data were confirmed in DISCOVER-1 (patients naive or previously treated with TNFi) and DISCOVER-2 (biologic-naive), two randomised controlled trials showing that GUS could significantly improve multiple domains of PsA involvement in these subgroups of patients (96, 97). Furthermore, this drug was efficacious in treating enthesitis and dactylitis (98, 99). Rahman *et al*. confirmed a significant and sustained improvement also in patients' fatigue (100).

Moreover, GUS had a favourable risk-benefit profile: few patients experienced serious infections, no study participant developed opportunistic infection or IBD (101, 102).

Finally, Sweet *et al*. found that GUS induced a robust reduction in acute phase proteins and in some cytokine (IL-17 and IL-22) levels, greater than the reduction observed with IL-12/23 inhibition related to UST (103).

Take home messages

- csDMARDs are the less expensive drugs, but with the lowest persistence on therapy rates (43);
- Tapering TNFi in SpA patients is associated to a high rate of flares (44);
- Biosimilar ETN and ADA seem to show efficacy and safety profiles substantially comparable with their originators (47-49);
- GOL was confirmed as a suitable therapeutic option for PsA patients, with globally good efficacy and safety profiles (53-58);
- In PsA patients TOFA was effective (particularly on articular involvement) and could exert a steroid-sparing effect, with a satisfactory retention rate and a good safety profile (59-61);
- The efficacy of UPA in PsA treatment was comparable with 15 and 30 mg, with a significantly higher AE rate with the higher dose (62, 63);
- More recent efficacy and safety data of APR are consistent with those already known; previous malignancies or bDMARD therapy could reduce cutaneous improvements (64-67);
- APR might be associated with lower healthcare costs than bDMARDs (68);
- Both IXE and SEC appeared effective and safe for PsA patients, both in clinical trials and in a real-life setting (69-87);
- SEC showed a good efficacy also in treating axial involvement and enthesitis, with sustained low rates of radiographic progression and good levels of retention rates (77, 78, 81-85);
- SEC immunogenicity seems to be not clinically relevant (87);
- UST generally improved disease activity measures, with a good safety profile; it may show lower efficacy in joint involvement or enthesitis, perhaps in relation with synovial molecular pathology issues (90-92);
- GUS could be a good option for patients with active PsA (95-103).

COVID-19

Although a report from a large Italian patient series showed a higher prevalence of COVID-19 in patients with autoimmune systemic diseases (104), a Spanish cross-sectional observational study reported that patients with chronic inflammatory arthritis had no higher incidence of COVID19 infection and the only factor significantly associated with fatality from COVID was older age (105).

Montero *et al*. described the clinical characteristic of patients with rheumatic diseases and COVID-19 to identify baseline variables associated with a severe infection requiring hospitalisation. In multivariate analysis, male sex, previous lung disease and glucocorticoids use were significantly associated with a higher risk of hospitalisation. However, neither specific diagnoses or exposure to DMARDs were associated with increased odds of hospitalisation (106). Similar results were found by Pablos *et al*., who identified as risk factors for hospitalisation aging, male sex and previous comorbidity such as obesity, diabetes, hypertension, CV and lung disease (107).

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